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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,899	06/04/2001	Nnochiri N. Ekwuribe	9233-54	5139

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	8

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,899	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40 and 41* is/are allowed.

6)☒ Claim(s) *1-6,8-15,17-39,42-48,50 and 52-67* is/are rejected.

7)☒ Claim(s) *7,16,49, and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Claims 4, 5, 32, 33, 35, 38, and 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 5, 32, 33, 35, 38, 54, and 55 are indefinite because it is not clear what are the lower limits to the ranges specified in the claims. For example, with respect to claim 2, assuming that "at least 2" is the lower limit to the number of PEG subunits, it is at best redundant to state that greater numbers of PEG subunits may be present. Assuming that 3 or 4 is intended to be the lower limit to the claimed ranges, then it is contradictory to also recite "at least 2". For analogous reasons, claims 5, 32, 33, 35, 38, 54, and 55 are also indefinite. There is no antecedent basis in the claims for the phrase "the polyalkylene glycol group" at claim 53, line 1. It is suggested that "group" be changed to "moiety" so that the claim terminology is consistent with that used in independent claim 52.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-6, 8-12, 15, 17-39, 42-48, 50, and 52-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-103 of copending Application No. 09/873,797. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '797

application anticipate instant claims 1-6, 8-12, 15, 17-29, 31-39, 42-48, 50, and 52-67. Note that the '797 application claims purely monodispersed mixtures of a drug coupled to a polyalkylene glycol moiety (see, e.g., claim 1) where the drug can be insulin (see, e.g., claim 64) and the polyalkylene glycol moiety can be polyethylene glycol (see, e.g., claim 21), and that the '797 application claims forming these conjugates (see, e.g., claims 95-102) by the same method claimed in the instant application. With respect to claim 30, while the '797 application does not claim the use of its insulin conjugates to treat insulin deficiency, it would have been obvious to one of ordinary skill in the art to use the insulin conjugates of the '797 application to treat insulin deficiency, because insulin deficiency is routinely treated with insulin and because it is routine to use conjugated protein or peptide therapeutics to treat diseases which are known in the art to be treatable with the unconjugated protein or peptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 13 and 14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-103 of copending Application No. 09/873,797 in view of the Hinds et al article (Bioconj. Chem., Vol. 11, pages 195-201) or Liu et al (U.S. Patent No. 6,323,311). The claims of the '797 application are as discussed in the above provisional obviousness-type double patenting rejection. The '797 application claims conjugates with insulin, but does not claim at what location on the insulin molecule the oligomers are attached. The Hinds et al article (see, e.g., the Abstract) teaches that conjugation of mPEG to the amino groups of either PheB1 or LysB29 results in conjugates which are more stable than commercially available preparations. Liu et al (see, e.g., column 7,

lines 48-55) teach conjugation of polyethylene glycol to the PheB1 residue of insulin, which increases the physical stability of such insulins. It would have been obvious to one of ordinary skill in the art to form the conjugates claimed in the '797 application with the oligomer attached to the amino groups of either PheB1 or LysB29 because the Hinds et al article and Liu et al suggest that these attachment points result in more stable preparations.

This is a provisional obviousness-type double patenting rejection.

5. Claims 59-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending Application No. 09/873,731 in view of the Hinds et al article (Bioconj. Chem., Vol. 11, pages 195-201) or Liu et al (U.S. Patent No. 6,323,311). Although the conflicting claims are not identical, they are not patentably distinct from each other. The '731 application claims the same method steps as are recited in the instant claims for forming the substantially monodispersed mixture of polymers having the structure of Formula III, but does not claim then activating the polymers and reacting them with calcitonin in order to form calcitonin conjugates. The Hinds et al article teaches forming PEG-insulin conjugates by first activating the PEG and then reacting the activated PEG with the insulin (see, e.g., page 196, column 2, first two paragraphs). Liu et al teach forming PEG-insulin conjugates by first activating the PEG and then reacting the activated PEG with the insulin (see, e.g., the Abstract). It would have been obvious to one of ordinary skill in the art to use the claimed method of the '731 application as a source of the PEG used in the Hinds et al article's and Liu et al's methods to form PEG-insulin conjugates because it is prima facie obvious to use the product of one process as the source of reactant for another process (see In re Kamlet, 88 USPQ 106 (CCPA 1950)).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 1-6, 8-14, 17, 19, 28-39, 42-48, and 50 are rejected under 35 U.S.C. 103(a) as being obvious over the Hinds et al article (Bioconj. Chem., Vol. 11, pages 195-201) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Hinds et al article teaches polyethylene glycol having a molecular weight of 750 or 2,000 daltons

conjugated to the amino group of either the PheB1 or LysB29 residues of human insulin. The conjugates are expected to have increased plasma half-lives, reduced immunogenicity and antigenicity, and improved resistance to proteolysis, and are used to treat insulin-dependent diabetes. See, e.g., the Abstract; page 195, column 1, first paragraph; and page 196, column 1, first and second full paragraphs. The Hinds et al article does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-insulin conjugates of the Hinds et al article using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Hinds et al article; because the use of discrete length PEG in the conjugates of the Hinds et al article would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been

expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

8. Claims 1-6, 8-13, 17, 19-23, 28-39, 42-48, and 50 are rejected under 35 U.S.C. 103(a) as being obvious over Liu et al (U.S. Patent No. 6,323,311) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Liu et al teach oligomers comprising polyethylene glycol conjugated to the PheB1 residue of human insulin. The polyethylene glycol can comprise from about 3 to about 400 PEG subunits. The oligomers can also comprise lipophilic moieties (see, e.g., claims 13 and 18, in which the $(CH_2)_p$, $(CH_2)_r$, $(CH_2)_m$, $(CH_2)_k$ groups correspond to Applicants' lipophilic moieties). The conjugates have increased stability, increased mean residence time, and attenuated immunogenicity and antigenicity. See, e.g., the Abstract; column 2, lines 35-39; column 6, lines 4-21 and 33-35; Example 1; and column 8, lines 11-19. Liu et al do not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-insulin conjugates of Liu et al using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates

according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Liu et al; because the use of discrete length PEG in the conjugates of Liu et al would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

9. Claims 1-6, 8-12, 15, 17-25, 28-39, 42-48, 50, and 52-57 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Ekwuribe teaches conjugates in which a polymer comprising a PEG moiety which preferably has more than 7 subunits and a lipophilic moiety is conjugated via a labile bond to a peptide, which can be insulin and which conjugation can occur at an amine group present on the peptide. Plural polymers can be conjugated to each peptide. Conjugation results in prolonged blood circulation and enhanced resistance to enzymatic degradation, relative to the peptide alone. See, e.g., the Abstract; column 6, lines 49-61; column 11, lines 19-20; column 12, lines 11-16 and 35-40; column 13, Conjugates 2 and 3; and column 14, lines 3-14 and 43-55. Ekwuribe does not teach the degree of substitution and the polymer size for insulin conjugates in particular. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, in order to maximize the desirable properties for the insulin conjugates of Ekwuribe. Ekwuribe does not

teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application 97/14740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the insulin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

10. Claims 1-6, 8-15, 17-25, 28-39, 42-48, 50, and 52-57 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-6, 8-

12, 15, 17-25, 28-39, 42-48, 50, and 52-57 above, and further in view of the Harris et al article (J. Macromol. Sci., Vol. C25, pages 325-373), the Hinds et al article (Bioconj. Chem., Vol. 11, pages 195-201) or Liu et al (U.S. Patent No. 6,323,311). As noted above, while Ekwuribe does not teach degree of substitution and the polymer size for insulin conjugates in particular, the Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-insulin conjugates of Ekwuribe in order to maximize the conjugates' desirable properties. Ekwuribe does not teach conjugation at the PheB1 or the LysB29 residue of insulin. The Hinds et al article teaches forming PEG-insulin conjugates by reacting activated PEG with the amino groups at PheB1 or LysB29 (see, e.g., the Abstract). Liu et al teach forming PEG-insulin conjugates by reacting activated PEG with the amino groups at PheB1 (see, e.g., the Abstract). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to conjugate the polymers of Ekwuribe to the amino groups of either the PheB1 or the LysB29 residues present in insulin because the Hinds et al article and Liu et al disclose that these residues are useful attachment points for forming stable insulin conjugates.

11. Claims 40 and 41 are allowed. Claims 7, 16, 49, and 51 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The prior art of record does not teach or suggest conjugates having the structures required

by instant claims 7, 40, 41, 49, and 51. With respect to instant claim 16, the prior art of record does not teach or suggest insulin conjugates having a relatively high dispersity coefficient in which oligomers are coupled to both the LysB29 residue and to the N-terminus at either A1 or B1. While such di-substituted conjugates are inherently produced in non-selective conjugation procedures involving insulin, the prior art of record provides no motivation or suggestion for one of ordinary skill in the art to isolate such disubstituted conjugates to the degree claimed by Applicants.

Claims 26, 27, and 58 are novel and unobvious over the prior art of record or any combination thereof, which does not teach or suggest oligomers having the structures recited in these claims conjugated to insulin.

The Coudert et al article (Synth. Comm., Vol. 16, pages 19-26) is deemed to be the closest prior art of record with respect to instant claims 59-67. However, the Coudert et al article does not teach or suggest the use of a mesylate activating group in reacting its ethylene glycol subunits with one another (see page 20).

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
February 14, 2003